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Haplophytine

Construction of the "Left Domain" of Haplophytine**

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Dedicated to Professor Madeleine M. Joullié on the occasion of her 80th birthday

Haplophytine (**1**, Figure 1) is an architecturally intriguing and synthetically daunting heterodimeric alkaloid endowed with insecticidal properties. Originally isolated in 1952 by Snyder and co-workers[1a–d] from the Mexican plant *Haplophyton cimicidum*, the structure of haplophytine was finally revealed in 1973 as a result of the pioneering studies of the groups of Cava,[1e,h] Yates,[1f,h] and Zacharias.[1f,g] The haplophytine molecule consists of a central indole moiety onto which two tetracyclic heterocycles are attached, the one on the "right" fused onto the indole system, and the one on the "left" bridged through a sterically demanding carbon–carbon bond (C9′–C15) to the aromatic nucleus of the indole. The two overlapping domains of the haplophytine molecule are designated as truncated haplophytine (**2**, "left domain", Figure 1) and aspidophytine (**3**, "right domain", Figure 1). While four total syntheses have already been reported for the naturally occurring aspidophytine (**3**),[2] beginning with Corey's brilliant synthesis in 1999,[2a] the "left" domain of haplophytine with its challenging connectivity to the indole moiety remains to this day as a thorny synthetic problem.[3] We now report the construction of compound **2** (Figure 1), a truncated version of haplophytine (**1**) housing the entire "left wing" skeleton of the natural product, including six of its rings and its C9′–C15 bond.

On the basis of biosynthetic considerations and degradation studies,[1h] we envisioned indole derivatives **4** and **5** (Figure 1) to be potential key building blocks for constructing

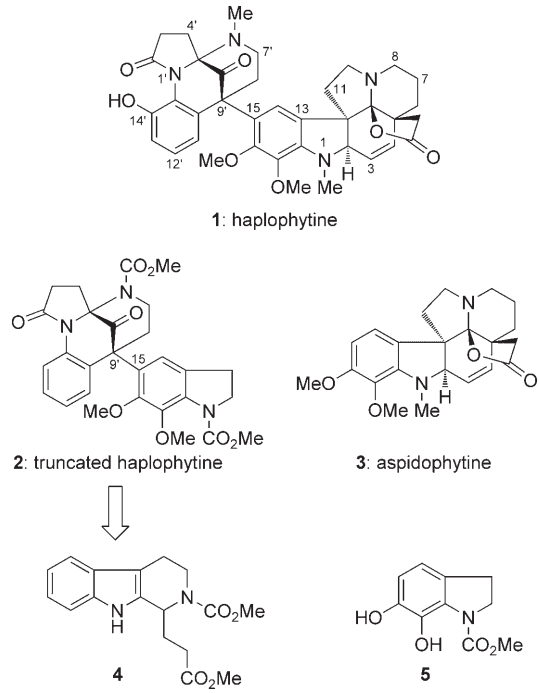

Figure 1. Structures of haplophytine (**1**), truncated haplophytine (**2**), and aspidophytine (**3**), and retrosynthetic analysis of **2**.

the required haplophytine skeleton. A possible scenario for their coupling to afford the desired but challenging carbon–carbon bond between them (C15–C9′, haplophytine numbering) would be to activate one of them with a suitable reagent towards nucleophilic attack and allow the other to act as an incoming nucleophile. To test this hypothesis, we set out to synthesize **4** and **5**.

Scheme 1 summarizes the construction of tetrahydro-β-carboline **4** starting with tryptamine (**6**). Thus, acylation of **6** with succinic anhydride, followed by methylation of the resulting carboxylic acid (MeOH, amberlyst-15) afforded methyl ester **7** in 80% overall yield. Dihydro-β-carboline formation within **7** under Bischler–Napieralski[4] conditions ($POCl_3$) gave the corresponding imine, reduction of which with $NaBH_4$ furnished, after nitrogen protection ($NCCO_2Me$) of the resulting secondary amine **8**, the desired tetrahydro-β-carboline **4** in 21% overall yield (unoptimized).

Scheme 2 depicts the synthesis of the other desired building block, diphenol **5**. Thus, the known phenol **9**[3] was benzylated (BnBr, K_2CO_3), and the resulting product was subjected to a Henry[5] reaction (nitromethane, NaOH) followed by elimination (Ac_2O, NaOAc) to afford nitroalkene **10** in 88% overall yield for the three steps. Reduction of **10**

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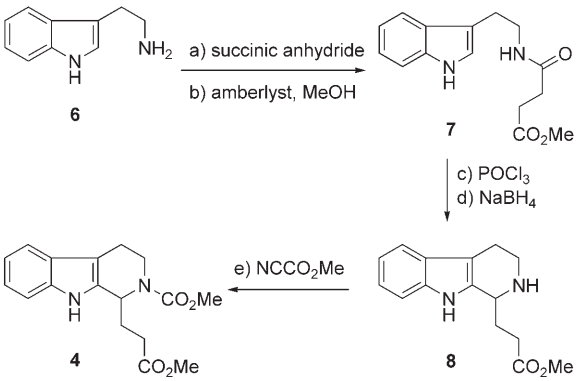
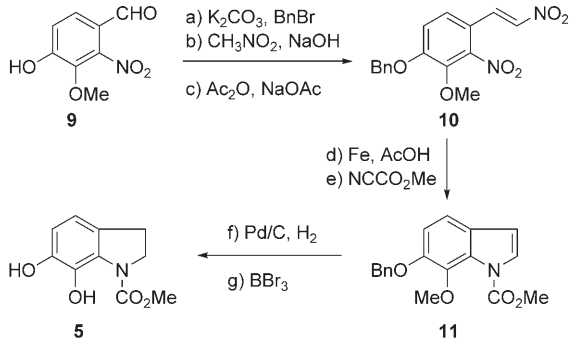
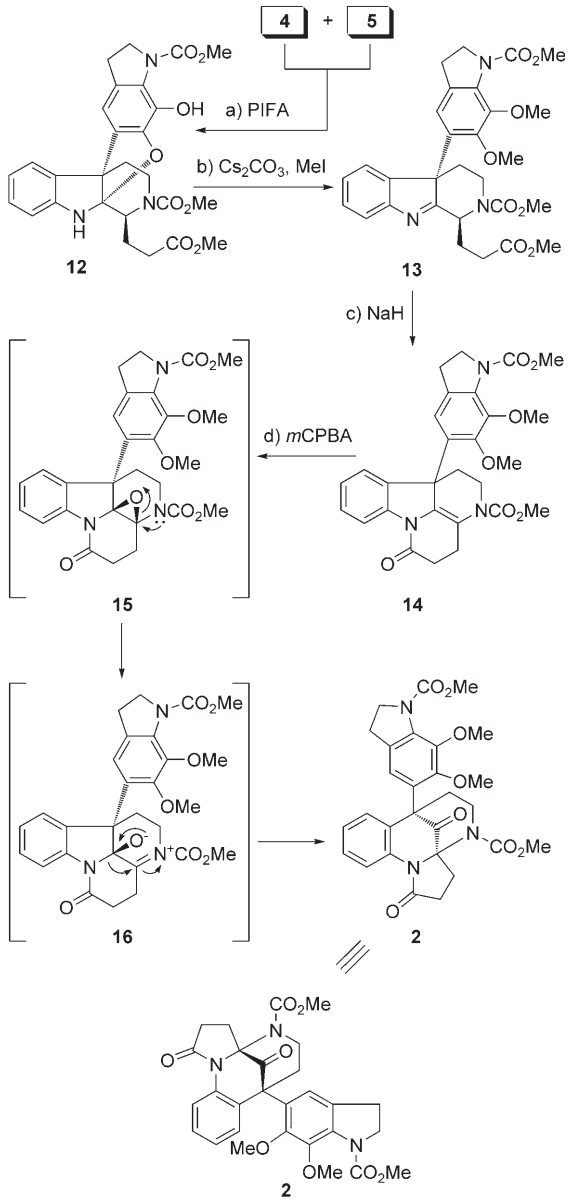


Scheme 1. Construction of tetrahydro-β-carboline **4**. Reagents and conditions: a) succinic anhydride (1.1 equiv), CH_2Cl_2, 23 °C, 19 h, 82%; b) amberlyst-15 (20% w/w), MeOH, reflux, 19 h, 98%; c) $POCl_3$ (7.0 equiv), benzene, reflux, 1.5 h, d) $NaBH_4$ (1.5 equiv), CH_3OH, 0 °C, 30 min, 42% for two steps; e) $NCCO_2Me$ (1.3 equiv), CH_2Cl_2, 0 °C, 19 h, 51%.



Scheme 2. Construction of diphenol **5**. Reagents and conditions: a) BnBr (1.3 equiv), K_2CO_3 (1.6 equiv), DMF, 0→23 °C, 14 h, 96%; b) CH_3NO_2 (1.8 equiv), NaOH (2.4 equiv), CH_3OH/H_2O (10:1), 0 °C, 30 min; c) NaOAc (2.1 equiv), Ac_2O, 140 °C, 30 min, 92% for two steps; d) Fe (21 equiv), AcOH/toluene (1:2), 110 °C, 30 min, 75%; e) KHMDS (0.5 M in toluene, 1.1 equiv), $NCCO_2Me$ (1.2 equiv), THF, −78 °C, 3 h, 96%; f) Pd (10% on activated carbon, 0.05 equiv), H_2, CH_3OH, 23 °C, 12 h, 95%; g) BBr_3 (3.0 equiv), CH_2Cl_2, −78→0 °C, 2 h, 90%. Bn = benzyl, DMF = *N*,*N*′-dimethylformamide, KHMDS = potassium hexamethyldisilazane.



Scheme 3. Total synthesis of the truncated haplophytine structure (**2**). Reagents and conditions: a) **4** (2.0 equiv), PIFA (1.2 equiv), CH_3CN/CH_2Cl_2 (9:1), −40→−30 °C, 48 h, 25%; b) Cs_2CO_3 (4.0 equiv), MeI (excess), DMF, 0→23 °C, 14 h, 60%; c) NaH (excess), THF, 0→23 °C, 14 h, 80%; d) *m*CPBA (1.4 equiv), $NaHCO_3$ (excess), CH_2Cl_2, 0 °C, 7 h, 65%. *m*CPBA = *meta*-chloroperoxybenzoic acid, PIFA = $PhI(CF_3CO_2)_2$.

(Fe, AcOH) led to the corresponding indole (75% yield), whose exposed nitrogen atom was protected as a carbamate ($NCCO_2Me$) to furnish indole derivative **11** in 96% yield. Reduction of indole **11** to its corresponding indoline with concomitant cleavage of the benzyl ether was achieved under catalytic hydrogenation conditions (95% yield), while cleavage of the methyl ether was performed with BBr_3 (90% yield), operations that led to the required diphenol **5**.

With the required components (**4** and **5**) in hand, we proceeded to find conditions for their coupling. After considerable experimentation, we discovered that reacting **4** and **5** in the presence of $PhI(CF_3CO_2)_2$ (PIFA) in acetonitrile/dichloromethane (9:1) at −40 °C resulted in their union, furnishing hexacyclic compound **12** in 25% yield (Scheme 3).[6] The structure of **12** (m.p. = 131–133 °C, from acetonitrile) was based on its spectroscopic data and was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Figure 2).[7] Apparently, after coupling of the two partners through initial activation of the diphenolic substrate followed by stereoselective nucleophilic attack from the indole component, the closest phenolic group collapsed upon the generated imine to form the observed oxygen bridge between the two domains of the product **12**. This undesired bridge was then ruptured by exposure of **12** to Cs_2CO_3 and MeI, conditions that also led to methylation of the two phenolic oxygen atoms, furnishing the pentacyclic imine **13** (60% overall yield). Treatment of the latter compound with NaH in THF caused isomerization of the

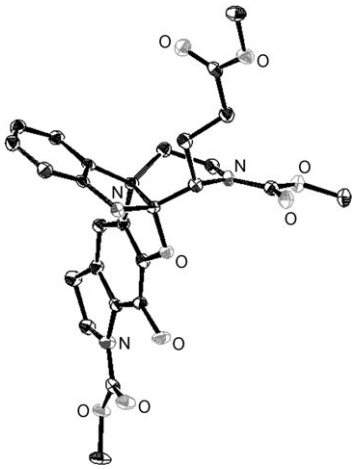


Figure 2. ORTEP drawing of **12**. Thermal ellipsoids are shown at the 50% probability level. One molecule of CH_3CN per molecule of **12** observed in the crystal lattice is omitted for clarity.

imine double bond and concomitant ring closure, leading to tetrasubstituted olefin **14** in 80% yield.

Substrate **14** was expected[8] from the outset to undergo, upon epoxidation, a cascade reaction involving regioselective epoxide opening and skeletal rearrangement to afford the targeted "left" nucleus of haplophytine (**2**) as shown in Scheme 3. Indeed, when **14** was treated with 1.4 equivalents of *m*CPBA in CH_2Cl_2 at 0 °C, it was smoothly converted into **2** (65% yield), presumably through intermediates **15** and **16**. Although the *anti* stereochemistry is shown arbitrarily in Scheme 3 for **15** and **16**, no evidence exists as to their stereochemistry, as these intermediates were neither characterized nor detected.[9] The structure of compound **2** (m.p. = 255–256 °C (decomp.), from benzene/acetonitrile) was based on its spectroscopic data (Table 1) and was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Figure 3).[7]

The described chemistry provides a synthetic pathway to the hitherto inaccessible "left domain" of haplophytine (**1**)

Table 1: Selected data for compounds **4**, **5**, **12**, **13**, **14**, and **2**.

4: $R_f = 0.70$ (silica gel, EtOAc/hexane 1:1); m.p. = 157–159 °C (CH_2Cl_2/hexane); IR (film): $\nu_{max} = 3472, 2969, 2506, 1654, 1614, 1482, 1254\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 11.17$ (s, 1H), 6.58 (d, $J = 8.7$ Hz, 1H), 6.57 (d, $J = 8.7$ Hz, 1H), 6.23 (s, 1H), 4.02 (t, $J = 8.1$ Hz, 2H), 3.85 (s, 3H), 3.01 ppm (t, $J = 8.1$ Hz, 2H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 156.2, 145.7, 132.6, 127.6, 124.7, 115.5, 110.9, 53.7, 49.1, 27.1$ ppm; HRMS (ESI): calcd for $C_{10}H_{12}NO_4$ $[M+H^+]$: 210.0761; found: 210.0775.

5: $R_f = 0.55$ (silica gel, EtOAc/hexane 1:1); IR (film): $\nu_{max} = 3321, 2953, 1733, 1677, 1439, 1409, 1229\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 9.05$ (s, 1H), 7.45 (d, $J = 7.9$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.13 (ddd, $J = 8.3, 7.2, 1.1$ Hz, 1H), 7.06 (ddd, $J = 7.9, 7.2, 1.0$ Hz, 1H), 5.31 (brs, 1H), 4.33 (brs, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.23 (brt, $J = 12.4$ Hz, 1H), 2.72–2.80 (m, 1H), 2.67–2.72 (m, 1H), 2.42–2.55 (m, 2H), 2.25 (dddd, $J = 14.3, 7.4, 7.4, 4.0$ Hz, 1H), 2.10 ppm (dddd, $J = 14.2, 10.1, 7.4, 7.4$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 173.3, 156.4, 136.4, 134.1, 126.9, 121.4, 119.1, 117.8, 111.0, 108.0, 52.1, 51.0, 51.0, 38.1, 30.4, 29.2, 20.9$ ppm; HRMS (ESI): calcd for $C_{17}H_{21}N_2O_4$ $[M+H^+]$: 317.1496; found: 317.1523.

12: $R_f = 0.33$ (silica gel, EtOAc/hexane 1:1); m.p. = 131–133 °C (CH_3CN); IR (film): $\nu_{max} = 3326, 2952, 1733, 1672, 1478, 1450, 1400\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 10.77$ (s, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.04 (ddd, $J = 7.7, 7.7, 1.2$ Hz, 1H), 6.73 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.69 (s, 1H), 6.62 (d, $J = 7.9$ Hz, 1H), 5.71 (brs, 1H), 4.72–4.68 (m, 1H), 4.05–3.95 (m, 2H), 3.84 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.41–3.37 (m, 1H), 3.09–3.02 (m, 1H), 3.01–2.93 (m, 2H), 2.55 (dd, $J = 14.3, 4.0$ Hz, 1H), 2.43–2.39 (m, 2H), 2.35 (ddd, $J = 14.1, 5.6, 5.6$ Hz, 1H), 2.17 (dddd, $J = 14.4, 7.2, 7.2, 5.5$ Hz, 1H), 1.74 ppm (dddd, $J = 14.3, 11.4, 7.1, 7.1$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 173.3, 157.0, 156.1, 147.8, 147.1, 132.4, 130.5, 128.6, 128.2, 128.0, 127.2, 122.3, 118.7, 109.5, 109.5, 107.8, 55.9, 55.8, 53.6, 52.0, 51.0, 49.4, 38.6, 30.7, 29.0, 27.4, 27.3$ ppm; HRMS (ESI): calcd for $C_{27}H_{30}N_3O_8$ $[M+H^+]$: 524.2027 found: 524.2072.

13: $R_f = 0.40$ (silica gel, EtOAc/hexane 2:1); IR (film): $\nu_{max} = 2952, 1728, 1702, 1582, 1444, 1405, 1384\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.58$ (d, $J = 7.8$ Hz, 1H), 7.34 (ddd, $J = 8.8, 7.3, 1.7$ Hz, 1H), 7.29 (s, 1H), 7.19–7.15 (m, 2H), 5.34 (dd, $J = 10.0, 4.2$ Hz, 1H), 4.12 (ddd, $J = 11.1, 8.5, 6.6$ Hz, 1H), 4.07–3.99 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 3.37 (s, 3H), 3.20 (ddd, $J = 14.3, 9.5, 2.9$ Hz, 1H), 3.08–3.02 (m, 3H), 2.97 (brs, 3H), 2.62 (dddd, $J = 14.3, 7.6, 7.6, 4.3$ Hz, 1H), 2.52–2.44 (m, 2H), 2.07–2.01 (m, 1H), 1.29 ppm (ddd, $J = 14.5, 8.9, 8.9$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 188.9, 173.3, 156.1, 156.0, 154.6, 149.9, 144.4, 143.4, 134.1, 131.2, 127.8, 127.5, 125.1, 122.4, 120.1, 117.3, 59.6, 58.7, 58.7, 55.2, 52.4, 51.9, 51.0, 50.9, 35.4, 31.3, 30.0, 29.0, 27.2$ ppm; HRMS (ESI): calcd for $C_{29}H_{34}N_3O_8$ $[M+H^+]$: 552.2340; found: 552.2393.

14: $R_f = 0.30$ (silica gel, EtOAc/hexane 1:1); IR (film): $\nu_{max} = 2951, 1702, 1677, 1464, 1442, 1379, 1341\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 8.12$ (d, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.26 (ddd, $J = 7.9, 7.9, 1.2$ Hz, 1H), 7.18 (s, 1H), 7.05 (ddd, $J = 7.5, 7.5, 1.1$ Hz, 1H), 4.10 (ddd, $J = 11.1, 9.0, 6.3$ Hz, 1H), 4.03 (ddd, $J = 11.0, 8.9, 7.3$ Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.64 (s, 3H), 3.57 (s, 3H), 3.52–3.49 (m, 1H), 3.44–3.38 (m, 2H), 3.27 (dd, $J = 13.7, 5.7$ Hz, 1H), 3.08–2.94 (m, 3H), 2.68 (ddd, $J = 16.3, 5.7, 2.3$ Hz, 1H), 2.48 (ddd, $J = 15.8, 15.8, 5.8$ Hz, 1H), 1.79 ppm (ddd, $J = 13.2, 13.2, 7.2$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 165.8, 155.2, 154.6, 151.1, 144.1, 140.3, 136.6, 134.5, 130.8, 130.3, 128.0, 124.1, 123.9, 117.2, 115.0, 59.8, 58.3, 52.4, 52.2, 51.2, 48.6, 41.3, 34.4, 32.7, 28.9, 23.8$ ppm; HRMS (ESI): calcd for $C_{28}H_{29}N_3O_7Na$ $[M+Na]$: 542.1898; found: 542.1910.

2: $R_f = 0.25$ (silica gel, EtOAc/hexane 1:1); m.p. = 255–256 °C (decomp) (C_6H_6/CH_3CN); IR (film): $\nu_{max} = 2950, 1754, 1705, 1443, 1379, 1128\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 8.14$ (dd, $J = 8.2, 1.3$ Hz, 1H), 7.28 (ddd, $J = 7.3, 7.3, 1.5$ Hz, 1H), 7.14 (s, 1H), 7.12 (ddd, $J = 7.9, 7.9, 1.2$ Hz, 1H), 6.91 (dd, $J = 7.9, 1.4$ Hz, 1H), 4.17–4.08 (m, 2H), 3.76 (s, 3H), 3.67–3.62 (m, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.36 (ddd, $J = 13.9, 7.0, 7.0$ Hz, 1H), 3.25 (ddd, $J = 14.0, 11.2, 6.3$ Hz, 1H), 3.08 (dd, $J = 7.8, 7.8$ Hz, 2H) , 2.95 (ddd, $J = 17.5, 11.3, 6.3$ Hz, 1H), 2.87 (s, 3H), 2.84 (ddd, $J = 12.9, 8.2, 6.8$ Hz, 1H), 2.61 (ddd, $J = 13.2, 6.6, 6.6$ Hz, 1H), 2.52 (ddd, $J = 15.6, 11.1, 4.6$ Hz, 1H), 2.28 ppm (ddd, $J = 14.0, 11.1, 4.5$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 196.3, 172.3, 155.4, 154.7, 149.4, 143.6, 135.9, 135.0, 133.6, 131.2, 130.5, 127.7, 127.1, 125.3, 120.0, 117.5, 81.6, 58.3, 58.2, 52.8, 52.6, 52.5, 51.3, 39.5, 36.6, 30.7, 29.0, 20.9$ ppm; HRMS (ESI): calcd for $C_{28}H_{30}N_3O_8$ $[M+H^+]$: 536.2027; found: 536.2075.

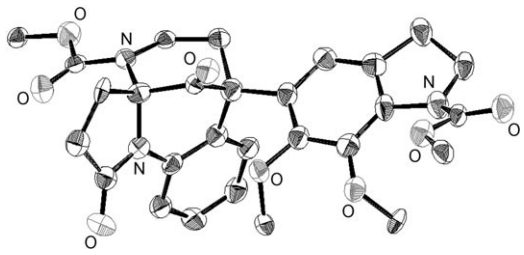


Figure 3. ORTEP drawing of **2**. Thermal ellipsoids are shown at the 50% probability level.

and should facilitate the total synthesis of this long-sought synthetic target.

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Keywords: alkaloids · natural products · nitrogen heterocycles · rearrangement · total synthesis

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[6] Similar reactions were reported by Danishefsky and co-workers, who observed, as an unintentional product and in unspecified yield, a similar product in their work towards phalarine (C. Chan, C. Li, Z. Fei, S. J. Danishefsky, *Tetrahedron Lett.* **2006**, *47*, 4839 – 4841), and by Harran and co-workers, who constructed a similarly crowded C–C bond between a phenol and an oxazole in their synthesis of diazonamide A (A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem.* **2003**, *115*, 5111 – 5116; *Angew. Chem. Int. Ed.* **2003**, *42*, 4961 – 4966).

[7] CCDC 645294 and 645295 contain the supplementary crystallographic data for compounds **12** and **2**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] This expectation was based on the elegant work of Cava and Yates who, in 1973, converted reversibly haplophytine to haplophytine dihydrobromide, a hydroxyiminium species.[1h]

[9] It should be noted that haplophytine dihydrobromide[1h,8] (corresponding to **16**) was proven by X-ray crystallographic analysis to display *syn* stereochemistry. Molecular models, however, appear to favor an *anti* approach on **14** suggesting formation of the *anti* epoxide. On the other hand, the *anti* epoxide corresponding to **15** appears to be more strained than its *syn* counterpart.

